Title of Project:

Enhancing an EMR-Based Real-Time Sepsis Alert System Performance through Machine Learning

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ABSTRACT: (250 words maximum)

Purpose: The aim of this project was to enhance an existing clinical decision support (CDS) tool using artificial intelligence (AI) techniques and implement it in our electronic health record (EMR).

Scope: We have an existing sepsis related CDS, Sepsis-Alert (SA). The objective of this study was to report the development, implementation and performance of a novel knowledge-based AI enhanced sepsis related CDS, Intelligent Sepsis-Alert (ISA).

Methods: The performance of SA was reviewed, and errors analyzed for opportunities to revise the model. Patients were partitioned into 14 separate risk groups and variables' thresholds were optimized using a genetic algorithm. The model was tested in consecutive retrospective cohorts of ED patients and then integrated into our hospital's EMR. ISA was then optimized and calibrated while functioning in the live EMR environment. Its performance was assessed using a 3-month sample of patients using ICD-10 coding as the gold standard for sepsis.

Results: The final model consisted of 12 variables and partitioned patients into 14 groups. The performance in the derivation phase resulted in a sensitivity, specificity and positive predictive value (PPV) of 83.3%, 91.1% and 89.7% without and 90.9%, 90.9% and 90.3% following partitioning. The mean and median time to identify sepsis was 68.9 ± 72.3 and 46.9 minutes respectively. In live validation the sensitivity was 77.8%, the specificity was 99.5% and the PPV was 57.3%.

Conclusion: Our novel computer based CDS alert resulted in moderate sensitivity while minimizing resulting false positives. Partitioning patients into groups based on demographic features improved performance.

Key words: artificial intelligence, sepsis, electronic health record, clinical decision support

PURPOSE

Our primary hypothesis was that Intelligent Sepsis Alert (ISA), an artificial intelligence enhanced version of the current Sepsis Alert (SA) would attain a sensitivity of at least 90% and increased positive predictive value of over 60%. The potential impact of this project is profound whereby death and morbidity could be greatly reduced while simultaneously decreasing alert fatigue that plagues current sepsis clinical decision support (CDS) tools. The primary objective of the study was to develop ISA into an accurate, understandable and reliable CDS model that will operate autonomously in the electronic medical record (EMR) with the functionality assist clinical staff to identify emergency department (ED) patients with sepsis in real-time. The secondary objectives assessed the feasibility and performance of partitioning of the patients into risk strata for sepsis and optimization of the model logic specific to the individual separate risk strata.

SCOPE

Sepsis is common in the U.S. It represents a healthcare epidemic that afflicts over 750,000 people annually.[1] It represents a host's dysfunctional response to infection and includes a spectrum of disease severity from mild (sepsis) to the most severe (septic shock).[2,3] Sepsis is expensive and costs approximately $16.7-20.3 billion annually and represents over 5% of total hospital costs in the U.S.[1,4-6] Its incidence is increasing by 1.5% per year and hospitalizations for sepsis increased from 143 to 243 per 100,000 persons between the year 2000 and 2007.[1,7] Sepsis is a national and international priority as demonstrated by the Surviving Sepsis Campaign (SSC) who strongly recommends early intervention and the Center for Medicaid and Medicare Services (CMS) who established sepsis as a core quality measure in 2015.[8 9-11]

Sepsis kills at a case fatality rate of 25% but despite this its recognition is challenging due to the heterogeneity of patients who may manifest a wide array of clinical presentations.[11-13] It is clear, however, that if sepsis patients are identified early and accurately, then delivering appropriate antibiotics and resuscitation will improve outcomes and resource utilization.[1,14] Unfortunately, significant barriers are common among nurses and clinicians with regards to both the recognition of sepsis and the urgency to delivery prompt care.[15,16] Expeditious, accurate recognition and intervention has been cited as being by far the biggest barrier to compliance.[17] Though the diagnostic criteria for sepsis appear relatively straightforward, the literature illustrates that sepsis is actually a diagnostic challenge and it is well documented that physicians commonly under-detect sepsis. [18,19] A major contributing factor is that many septic patients may initially present without organ dysfunction or evidence of shock and only develop these during their ED stay, making early clinical recognition challenging.[12,20,12,21]

Computerized CDS programs are now commonly available to assist with sepsis screening within the EMR. However, they are often built on rudimentary logic that are applied indiscriminately to patients no matter how different they are. Furthermore, many were designed for ICU or medical wards and only a few were tailored specifically to the ED in the initial crucial hours of patient presentation when clinical data is relatively scant.[22] The reported sensitivity of these CDS software is 40-60%, with positive predictive values of 20%-54%.[21,23] This low accuracy results in excessive false negatives, leading to delayed care in unrecognized sepsis patients and *alert fatigue* secondary to excessive false positives which desensitizes caregivers to all alerts.[24]

One major limitation of the existing alert system in our hospital system and all other sepsis CDS tools in the literature is that they lack any mechanism to learn from its past erroneous sepsis screening decisions and may repeat the same mistakes again and again on new patients. Another major limitation of all the CDS tools for sepsis, including our *SA*, is that the numbers of decision rules and variables in the rules are fixed, so are the number of intervals and the interval terminals that divide the range of each variable. Consequently, that means that all the patients are treated in the same way regardless of their age, gender, comorbidities or other factors

The PI and engineering Co-I of this proposal collaboratively developed a CDS software named Sepsis-Alert (SA), which has been operating in our Cerner Millennium™ EMR since October 2014. Sepsis-Alert was specially designed to identify sepsis in ED as early as possible and uses sepsis specialist's decision rules to calculate a score based on vital signs, labs, demographics, and nurse assessments. It delivers an automated alert message to a dedicated pager and email accounts when the score satisfies pre-determined criteria. Our analysis of over

25,000 cases shows that SA has a sensitivity and specificity of 80.3% and 98.6%, respectively, and a positive predictive value of 20.4% for identifying adult sepsis patients in the ED.

We proposed to substantially improve SA through such artificial intelligence techniques as fuzzy logic (for handling ambiguity and uncertainties) and genetic algorithms (for optimizing parameters). The proposed innovative software, named Intelligent Sepsis-Alert (ISA) will continuously monitor the EMR of every ED patient to identify patients likely to have sepsis. The ISA (1) assigns the patient to a category based on his/her characteristics, (2) apply decision rules, variables and other parameters of that patient category to compute a score, and (3) use the score to make a sepsis alert decision and notify a health care provider in real-time.

Review of the original Sepsis-Alert. The primary goal of the Sepsis-Alert was to identify ED patients highly likely to have sepsis, severe sepsis or septic shock within the initial 6 hours of arrival and while still in the ED. Its development and implementation were funded by Blue Cross Blue Shield of Michigan Foundation in a previous grant. The basic logic rules were initially provided by sepsis experts and supported by the literature. A group of original decision-making rules was provided from the expert physicians as a basis for the decision-making based on the variables selected for inclusion (Table 1).

Criteria	Points	Comment
If either RR > 23 OR HR > 110	1	
T > 38.3	1	(2 points if combined with one of the critical conditions or Age >=75 years)
WBC > 15.0 or Bands > 5%	1	(2 points if combined with one of the critical conditions or Age >=75 years)
Lactate >= 4.0	3	
Critical condition(If any: ESRD[a] or NH[b] resident or HIV or SBP < 90)	2	
Age >= 75 years	1	

Table 1: Sepsis-Alert logic. Alert delivered for any score of > 2.
a – end stage renal disease; b – nursing home.

Nursing home residents presenting to the ED for care have a high prevalence of sepsis which is why this was included as one of the variables. Unfortunately, in our EMR there is no unique and abstractable data point available to easily identify these patients. This is the primary reason for including Schimdt's Fall Risk (SFR), a routine nursing assessment, in the model as a surrogate marker for patients who are likely nursing home residents. SFR assessment is required nursing documentation by ED nurses and is performed multiple times daily for inpatients. The responses are discreet and assess four elements of the patients' physiologic status, two of which (Mentation and Mobility) were used. For purposes of these models, any patient with a 'Mentation' of 'Confusion at all times' or 'Comatose, unresponsive' *plus* a 'Mobility' of 'unable to transfer or ambulate' was considered a nursing home patient or a nursing home patient equivalent. The kappa statistic between the Schmidt's Fall Risk and nursing home status (from manual chart review) was 0.85 in a subset of patients, providing a strong level of confidence in its validity.

METHODS

Rule Modification Phase. The initial development of ISA was based upon SA and its historical cases reviewing for errors and opportunities to improve. We took a random sampling of the charts from the live-production and reviewed 1,000 false negative and false positive charts to identify major themes and root cause of errors. Errors were codified based on likely source:

- Coding error – ICD codes not consistent with charted diagnosis
- Data entry – Error with respect to vital sign documentation or documentation of co-morbidities
- Documentation – Documentation with respect to physician charting
- Logic – Error attributed specifically to model's logic.

Intelligent Sepsis Alert (ISA) was designed to be significantly enhanced version of SA and was designed to operate in similar fashion. The same EMR and initial EMR inputs and variables used by SA were used by ISA. The ISA logic was then modified accordingly as appropriate in response to the review of the errors. Each of the continuous variables' thresholds were then optimized to maximize sensitivity and positive predictive value for identifying sepsis in our derivation cohort.

ISA functions in real-time in conjunction with the live DMC EMR environment and constantly monitors patients. It issues an electronic alert to the healthcare providers once it finds that a patient satisfies the sepsis screening criteria. Only one alert is permitted per patient – ISA stops monitoring a patient once an alert has been issued for him/her. Substantial alert performance gain is expected for ISA owing to the three new components in Fig. 1, which will (1) classify patients into categories, (2) apply different sets of decision rules, variables and intervals for variables to different categories of patients, and (3) apply a different threshold to accumulated sepsis points for different patient category. The categories, decision rules, variables, intervals for variables and thresholds can all be adjusted offline.

As shown in Figure 1, there are seven blocks in the Intelligent Sepsis-Alert which are coded in two colors. Three are in white, which represent new components that do not exist previously. The remaining four blocks are in blue and their functions are very much like those in SA described above.

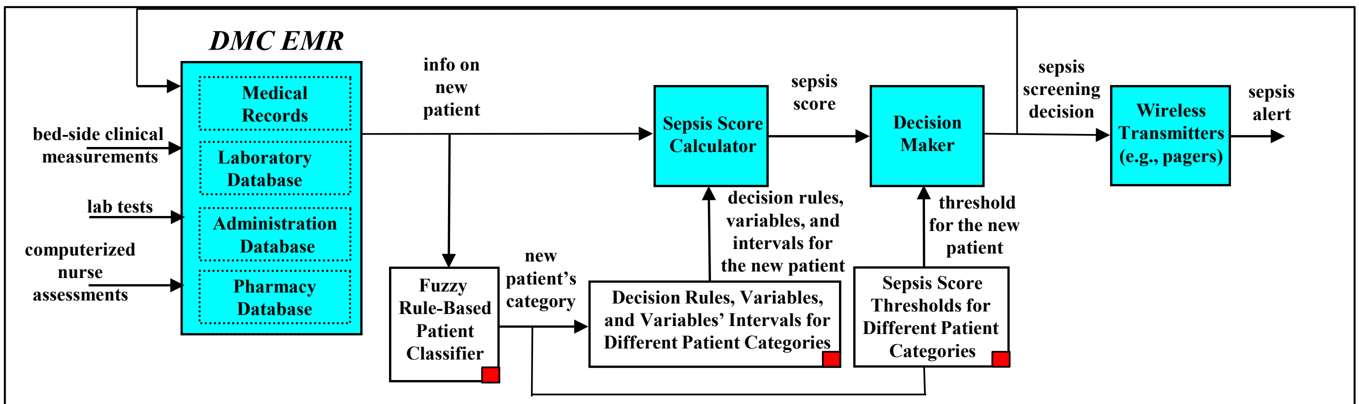

Figure 1: Structure of the original Sepsis-alert and of the new Intelligent-Sepsis system.

Partitioning. At present, identical variables, intervals for variables, decision rules and sepsis score threshold of *Sepsis-Alert* are indiscriminately applied to all patients regardless of age or co-morbidities. We addressed this weakness by partitioning patients into patient categories according to patient attributes and physician clinical knowledge. The 12 original variables, intervals for these variables, decision rules and sepsis score threshold used have delivered satisfactory clinical performance and were used as "initial conditions" and assigned to all the patient categories. This means when ISA began operating, all the patient categories shared the same setting. Their settings, however, started to evolve and may become different over time through the optimization process.

The 12 variables original variables served as input to 'Fuzzy Rule-Based Patient Classifier', which is a new component. This component is needed because one diagnostic difficulty as described above in the Significance section is that due to the high heterogeneity of sepsis, the implication of each of the variables may be strongly correlated to the context (demographics, co-morbidities, etc.) of the patient. Sepsis-Alert and all other similar systems treat all patients uniformly regardless of their age, comorbidities or other factors, which is counterintuitive to the thought process of a healthcare provider.

One optimization mechanism is 'Genetic-Algorithm-Based Optimizer' for 'Decision Rules, Variables' Intervals, and Thresholds', which optimizes decision rules, variables' intervals, and sepsis score thresholds of different patient categories though guided stochastic search conducted by a genetic algorithm. This was performed one category a time and covered all patient categories. An objective function was established, and it was the same for all the categories. It was used by the genetic algorithm to evaluate fitness of a new generation of the adjustable parameters in ISA. The function penalized occurrences of false positives and false negatives while rewarding correct decisions (e.g., a weighted sum function). To make the optimization process more efficient, we add constraints for ‘GA-Based Optimizer’ which set parameter search boundaries for the genetic algorithm. Decision rules and thresholds were optimized through improved point assignment.

During the optimization operation using historical cases, all the adjustable parameters were varied by the genetic algorithm within the constraints to minimize the objective function value (i.e., minimize the overall errors). The well-known elitism principle was adopted to ensure alert performance produced by a new generation is at least as good as that attained by the previous generation. One constraint imposed on the assignment is that the resulting rules must make clinical sense to the sepsis experts.

Every patient category defined in the ‘Patient Classifier’ has its own sets of variables, intervals for variables, and/or decision rules that are most suitable for the patients in the category. These sets are stored in the ‘Decision Rules, Variables, and Variables’ Intervals for Different Patient Categories’ component, which employs patient’s category to find the category’s corresponding decision rules, variables, and variables’ thresholds. The thresholds are stored in ‘Sepsis Score Thresholds for Different Patient Categories’.

The variables, intervals for variables, and decision rules corresponding to the patient’s category is sent to ‘Sepsis Score Calculator’. The Calculator will use them to compute a sepsis score in a way similar to *Sepsis-Alert* does. The score will then be compared by ‘Decision Maker’ to a threshold specific to the patient category to translate the score into a Yes or No “sepsis screening decision.” If decision is ‘Sepsis|No’, then no alert will be issued, and the decision will not be saved in the EMR. On the other hand, if decision is ‘Sepsis|Yes’, then the decision will be saved in the EMR and will automatically send an electronic alert email. No work was needed on this part of the system as it is presently functioning clinically.

Retrospective Derivation Phase. In this phase, a retrospective data set of initially 2,000 case (50% sepsis and 50% non-sepsis) was used to further refine the ISA. The initial 1,000 adult (>= 18 years) cases were selected from the EMR based on ICD-9 codes and were age matched with 1,000 adult age-matched admitted patients as controls. Each patient chart in this cohort was reviewed to for the presence of sepsis based on clinical criteria (Sepsis 2.0 – SIRS based criteria). Each case was then recategorize as sepsis (Yes|No) based on the chart review. The performance of the model was then assessed based on partitioning (with vs. without), by optimizing the variables individually in each category versus optimizing the overall score (and keeping the variable thresholds set). Errors were reviewed by point accruement, and patient group and adjustments made to the model accordingly. Finally, as a benchmark comparator, using MATLAB Classification Learner we compared performance of this model to 23 separate dedicated machine learning techniques.

Retrospective Test Phase. In this phase, a larger retrospective data set which included one year of sepsis cases selected, now based on ICD-10 codes and was matched with a random one year sample of non-sepsis cases admitted to the hospital from the ED for a target cohort size of 8-10K. Due to the size of this sample, individual chart adjudication was not possible and therefore the ICD-10 coding was used as the gold standard for diagnosis. Errors were again reviewed by point accruement, and patient group and adjustments made to the model accordingly. In this phase, multivariate logistic regression was used to determine the value of ISA model’s variables and to explore for potential additions.

Implementation Phase of ISA into DMC’s EMR. Drs. Sherwin and Ying have worked successfully with the DMC Information Technology (IT) department and had full support and cooperation with this project. The process of implementation included meetings and conference calls with the DMC IT director and the lead software programmers to establish the statement of work, a progression plan of tasks, and criteria for completion. Additionally, approval at the system level included conference call meetings with both local and national hospital system leadership. Regular programming meetings were attended by the IT leadership; the project programmers addressed any programming issues. The initial “build” occurred in the EMR test environment, which represents an operational clone of the live environment with the exception that it only contains fictional test patients. Components of ISA were then assessed individually first, followed by the entire module, within the test EMR environment to ensure they functioned properly.

Due to the prior experience, we have first-hand knowledge on the strengths and shortcomings of EMR programming environment with regard to adding a new user-defined function. We have taken advantage of this knowledge and designed ISA in such a way that it will be relatively easy to be implemented into the EMR. Our approach is to use lookup tables. Actually, all three new functions in Fig. 1, namely “Fuzzy Rule-Based Patient Classifier” (it is converted to Patient Category Lookup Table), “Decision Rules, Variables, and Variables’ Intervals for Various Patient Categories,” and “Sepsis Score Thresholds for Different Patient Categories” can be, and will be, implemented as multi-dimensional lookup tables. “Sepsis Score Calculator” is a basic calculator while “Decision Maker” is just a comparator. Therefore, there is no complex algorithm and all the operations are simple. Thus, as far as the implementation is concerned, ISA can be considered as a relatively straightforward upgrade from Sepsis-Alert. The expected timeline for the program implementation was few weeks.

Live Validation Phase. In the live validation phase, the final data for prospective analysis included all adult patients (>= 18 years at time of visit) seen in the ED of Sinai Grace hospital (Detroit, Michigan) between (inclusive) the dates of August 16th, 2018 and October 31st, 2018. The gold standard used for sepsis in the phase was based on ICD-10 coding. The model’s overall performance with respect to partitioning and identifying sepsis patients were reported. As in previous phases, error checking was performed to identify route causes.

RESULTS

Rule Modification Phase. This phase began by assessing and building upon our original model, Sepsis-Alert, which was already running in the EMR of the Detroit Medical Center since 2014. We reviewed 1,000 of randomly selected cases under the SA to determine thematic root causes of errors for potential correction.

In the review of the errors, several false negatives were attributed to patients who were at high sepsis risk due to reasons other than what SA defined as nursing home equivalence. Upon reviewing the Problem Lists available in the EMR, we also included patients with paraplegia and multiple sclerosis. This can be a complex process to be inclusive of all the possible data points as there are multiple results that indicate the presence of various co-morbidities of interest. We ultimately decided on including the following co-morbidities: end stage renal disease (13 diagnoses in Problem List), paraplegia (18 diagnoses), decubitus ulcer (8 diagnoses) while there is only one that represents the presence of multiple sclerosis. Therefore ‘Nursing home equivalence’ in addition to the SFR based definition, ISA now included any patient with evidence multiple sclerosis, decubitus ulcer or paraplegia on their EMR Problem List in the NHE category. Historically sepsis and infection are a very common reason that result in ED visits for NH residents. As such we tested a stand-alone rule that would count all NHE patients as sepsis which resulted in poorer accuracy of the model. Therefore, the NHE variable remained only as a variable to categorize patients.

We had also considered using either a history of sepsis or history of stroke as well, but ultimately decided against it as the data revealed many of these patients actually had transient ischemic attacks (not a stroke) or the stroke history being recorded was unverified and therefore unreliable. A history of sepsis also did not provide added value beyond the comorbidities already being used. A history of HIV was utilized in the original SA rule, but was removed as it added no value to the model performance.

The error review resulted in a deeper understanding of the patient types and characteristics that mimicked sepsis physiology in the EMR. Two variable limits were established including ignoring any heart rate > 170 (this is generally due to an arrythmia and not sinus tachycardia) and ignoring any lactate acid > 10 (these are more often due to cardiac arrest then sepsis). For the variable thresholds, the model would still consider the patient but would not use either variable if it exceeded the set limit.

Common sepsis mimics (patients that often result in false positive alerts) include victims of trauma, diabetic ketoacidosis, COPD, cardiac arrest and respiratory failure. Based on the review, several new rules were considered. Patients with higher troponins tended to have primary diagnoses of cardiac ischemia and not sepsis. The investigators considered excluding patients with troponins above a certain threshold from the logic however it is not uncommon for patients with septic shock to demonstrate global ischemia and result in elevated troponins as well. We also considered excluding any patient with elevated glucose values. We considered manually adjusting the temperature threshold in response to the error review but elected to allow this part of the model to be informed primarily by the genetic algorithmic optimization. Additional considerations for model modification that were not ultimately implemented included extra weighting for extremely elevated WBC’s, including patients on active chemotherapy, extra weighting for the presence of multiple co-morbidities and adding history of intravenous drug use to the list of co-morbidities of interest.

We determined that a number of false positives were actually major trauma patients who had similar physiologic derangements as sepsis patients. It was discovered that one data element almost universally present in all major trauma evaluations, but not in most sepsis evaluation is the ordering or a serum alcohol level. In exploring this, we considered eliminating trauma patients using alcohol levels. Though it was very uncommon for patients with alcohol levels > 150 mg/dL to be adjudicated with sepsis, alcohol levels did not ultimately result in any significant reduction of false positives related to major trauma. Therefore, it was decided not to implement the alcohol rule.

Retrospective Derivation Phase. Our goal was to build the ISA model based on cases individually adjudicated by chart review by a sepsis expert. The reason for this is that ICD coding (in this case ICD-9) can be occasionally inaccurate. This phase included a cohort of patients with – originally 1,000 septic patients from a five-year period and a randomly selected cohort of non-sepsis patients over the same time period.

Following elimination of duplicate charts, and excluding children, the final number included a total of 1,887 patients (912 septic and 975 non-septic). These charts were selected based on ICD-9 codes which were the standard at the time. When this grant was submitted, the standard was still the SIRs based criteria and suspected or confirmed infection as oppose to SOFA based criteria (Sepsis 3.0). Sepsis 3.0 is still not universally adopted and at the time to this writing and CMS still adheres to the SIRS based criteria for sepsis diagnosis.

Charts were individually adjudicated for presence of sepsis as a primary or secondary condition for presentation to the hospital. This included suspicion of an infection plus two SIRSs criteria within the initial 6 hours. Through individual chart review, we determined several sources of errors leading to a significant proportion of false positives and false negative cases. This included modification of variable thresholds and expansion of critical conditions that put patients at risk for sepsis: specifically including active multiple sclerosis and a paraplegic state. Eighty-nine patients (4.7%) were recategorized base on this review; either from Sepsis|Yes to Sepsis|No or the reverse.

Partitioning Phase. Partitioning of the patient's cohorts was done based up known risk factors for sepsis and machine intelligence. Some of these were included in the original model and some were newly introduced. The major risk themes include patients who are bed bound, residents of nursing homes and patients with indwelling catheters for chronic hemodialysis. These patients were identified using the 'Problem List' in each patient's EMR. The Problem List pulls data and diagnoses from several sections of the EMR and compiles a comprehensive list of diagnoses that apply to each patient. The disadvantage is that this relies on human input and accuracy of the data and may not include patients new to the system or with new diagnoses for which the data has no yet been input into the EMR. Furthermore, temporary diagnoses (short term dialysis, for example) may result in a false indication that a patient is receiving ongoing chronic dialysis if this is not manually removed from the Problem List.

Patients were then partitioned in 12 separate groups based on age and sepsis risk factors (Table 2 and thresholds of each variable was set to a default prior to optimization. Due to group size, we split two into two separate groups and therefore ended up with a total of 14 groups. Using the genetic algorithm, thresholds were optimized across each of the fourteen groups to prioritize sensitivity, first, followed by positive predictive value (Table 3).

	Step I: Grouping Variables			Step II: Predictor Variables						
Patient Group	**Age**	**NHE[a]**	**ESRD**	**V1** (RR)	**V2** (HR)	**V3** (T)	**V4** (WBC)	**V5** (Bands)	**V6** (Lactate)	**V7** (SBP)
1	< 60	Yes	Yes	23	110	38.0	15,000	10%	4.0	3.0
2	< 60	Yes	No	23	110	38.0	15,000	10%	4.0	3.0
3	< 60	No	Yes	23	110	38.0	15,000	10%	4.0	3.0
4	< 60	No	No	23	110	38.0	15,000	10%	4.0	3.0
5	60-79	Yes	Yes	23	110	38.0	15,000	10%	4.0	3.0
6	60-79	Yes	No	23	110	38.0	15,000	10%	4.0	3.0
7	60-79	No	Yes	23	110	38.0	15,000	10%	4.0	3.0
8	60-79	No	No	23	110	38.0	15,000	10%	4.0	3.0
9	>79	Yes	Yes	23	110	38.0	15,000	10%	4.0	3.0
10	>79	Yes	No	23	110	38.0	15,000	10%	4.0	3.0
11	>79	No	Yes	23	110	38.0	15,000	10%	4.0	3.0
12	>79	No	No	23	110	38.0	15,000	10%	4.0	3.0

Table 2: Group categorization based on age, nursing home and dialysis. Additional variables list the current thresholds that will be modified in Specific Aims 2 and 3, resulting in individualized group logic

	Step I: Grouping Variables			Step II: Predictor Variables							
Patient Group	**Age**	**NHE[a]**	**ESRD**	**V1** (RR)	**V2** (HR)	**V3** (T)	**V4** (WBC)	**V5** (Bands)	**V6** (Lactate)	**V7** (SBP)	**V8** (Score)
All		Default value		23	110	38.0	15,000	10%	4.0	90	3.0
1	< 60	Yes	Yes	30	114	38.0	12,100	10%	1.4	83	3.0
2	< 60	Yes	No	21	126	38.2	12,300	10%	1.5	99	3.0
3	< 60	No	Yes	21	114	38.5	14,100	10%	1.3	84	3.0
4	< 50	No	No	27	111	38.0	12,800	10%	1.8	98	3.0
5	51-59			30	114	38.1	15,200	10%	1.5	98	3.0
6	60-79	Yes	Yes	30	114	38.0	12,100	10%	1.4	83	3.0
7	60-79	Yes	No	21	90	38.0	12,100	10%	1.6	99	3.0
8	60-79	No	Yes	30	114	38.0	12,100	10%	1.4	83	3.0
9	60-69	No	No	22	100	38.1	16,800	10%	1.8	90	3.0
10	70-79			22	91	38.0	12,200	10%	1.4	98	3.0
11	>79	Yes	Yes	30	114	38.0	12,100	10%	1.4	83	3.0
12	>79	Yes	No	22	95	38.0	13,100	10%	1.5	97	3.0
13	>79	No	Yes	30	114	38.0	12,100	10%	1.4	83	3.0
14	>79	No	No	22	125	38.2	13,300	10%	1.7	96	3.0

Table 3: V8 is fixed; V5 is also fixed during GA optimization process due to missing bands data
[a]NHE: Nursing Home Equivalent, (NH resident, paraplegia or multiple sclerosis)

At this stage the ISA model that was tested and modified during the remainder of the proposal is below.

Intelligent Sepsis Alert: Final Logic

Step I:
The following rules are applied to a patient AFTER he/she is classified into one of the 14 groups according to the criteria in Table 3 so that V1-V8 of this patient's particular group will be used in the rules below.

Step II:

	Points
Rule 1: If Respiratory rate > V1 *or* heart rate > V2 *(Ignore HR >=170)*	1
Rule 2: Temperature > V3 Celsius	1
Rule 3: White Blood Cell. > V4 *or* Bands >= V5	1
Rule 4: Lactate >= V6 *(Ignore Lactate >= 10)*	2
Rule 5: Systolic blood pressure < V7	2

Logic Function:
- The rules should only apply to patients based on the initial 6 hours of data from ED registration.
- Any point total of V8 or greater should trigger the ISA to fire. Once the alert fires for a patient – it should not fire again for the patient.
- Rules are based on all of the patient data up until ED disposition or 6 hours following presentation whichever comes first and points are cumulative.
- A rule can only accrue points once, after which the rule cannot contribute to any further point accumulation.
- Nursing Home Equivalent patient is defined by either of the following the following:
  - IF - in Problem List - patient has indications of one of more of the following: End stage renal disease, Paraplegia or Multiple sclerosis. *OR*
  - IF ['Mobility' = 'Unable to ambulate or transfer] AND ['Mentation' = 'Comatose, unresponsive' OR 'Confusion at all times'] on the nursing evaluation, Schmidt's Fall Risk.

The performance of this model on this initial data set resulted in a sensitivity, specificity and PPV of 83.3%, 91.1% and 89.7 % without and 90.9%, 90.9% and 90.3% following patient partitioning into different groups. If we optimized the necessary score and kept the variable thresholds set at their default (Table 2), the sensitivity was 81.4%, the specificity was 89.5% and the PPV was 87.9%. For 9 of the 12 patient groups including 467 patients (24.7%), the sensitivity of 100%. The remaining three groups had sensitivities of 88.8% (n = 730; 40%), 97.1% (n=189; 10%) and 92.5% (n=501; 30%).

The model performance was broken down by patient group to determine whether or not there was clustering of errors within any specific group. There was a balanced distribution of patients among the fourteen groups. There appeared to be no over-representation of errors within any specific patient group. In the derivation group. The mean points for true positive was 5.79, the mean for false positives was 4.39. The mean for true negatives was 0.54 and the mean for false negatives was 1.66.

To evaluate the false positives and false negatives we focused on false negatives with two points and false positives with three points or greater. There were 128 false positive patients with a score of 3 or greater. The combination of SBP < 90 mmHg and HR/RR accounted for 31.4% of all false positives. This is physiologically understandable as hypotension has a wide spectrum of etiologies. Furthermore, the HR/RR rule contributed to 70.1% of all false positive when combined with any other variable. Tachycardia and tachypnea are common finding in a many ED patient, particularly those with trauma or respiratory conditions. Of those non-sepsis patients who scored 2 points were just below the threshold, zero of these patients had WBC and T scored. A total of 26 patients were adjudicated as sepsis yet only scored one point on the model. There were 6 patients with sepsis who scored 0 points on the model.

Compare to 23 Machine learning techniques. In the process of refining our model to determine a benchmark standard for performance, we investigated various methods of machine intelligence to analyze our data set. We compared the performance of several dedicated machine-learning techniques with our CDS sepsis alert to identify ED patients with sepsis. The performance of a selection of the twenty-three machine learning techniques are reported in Table 4. From all of the techniques, the best sensitivity was 92.3% and the best specificity was 94.5% and the best PPV was 93.5%. These machine-learning techniques are generally too complex to build into an electronic medical record; however, lessons may be derived from them to guide future CDS tools.

Model Name	Sensitivity	Specificity	PPV
Complex Tree	86.8	89.3	88.4
Linear Discriminant	84.1	93.2	92.1
Quadratic Discriminant	87.1	90.4	89.4
Logistic Regression	88.3	91.1	90.2
Linear SVM	88.5	91.0	90.2
Quadratic SVM	89.8	90.9	90.2
Fine KNN	84.9	88.3	87.2
Medium KNN	91.1	90.8	90.2

Table 4: Performance of selected machine intelligence models on the 1887 patient data set.

The mean time to 'fire' for ISA in this cohort was 68.9 ± 72.3 minutes. The shortest time was 0.0 minutes, the longest time was 357.2 minutes (there is s 6 hours/360 minute limit to ISA) and the median time was 46.9 minutes. When the machine learning techniques were limited to 2 and 1 hour of data versus using 6 hours of data, their performance markedly deteriorated (Table 5).

		6-hour EMR data				2-hour EMR data				1-hour EMR data	
Name	**Sn**	**Sp**	**PPV**		**Sn**	**Sp**	**PPV**		**Sn**	**Sp**	**PPV**
Medium Tree	88.2	88.5	87.8		84.4	84.8	83.9		80.6	86.9	85.2
Linear Discriminant	84.1	93.2	92.1		79.2	91.6	89.8		71.9	89.9	87.0
Quadratic Discriminant	87.1	90.4	89.4		82.5	90.6	89.1		69.4	91.9	88.9
Logistic Regression	88.3	91.1	90.2		84.6	90.5	89.2		77.6	87.3	85.1
Linear SVM	88.5	91.0	90.2		83.7	91.7	90.4		76.8	88.3	86.0
Quadratic SVM	89.8	90.9	90.2		86.5	91.3	90.3		79.1	91.0	89.1
Fine KNN	84.9	88.3	87.2		80.5	86.3	84.6		77.3	80.9	79.1
Medium KNN	91.1	90.8	90.2		84.4	91.4	90.2		82.3	85.6	84.3

Table 5: Selected machine learning technique performances when the programs are limited to 1 or 2 hours of data as compared to 6 hours.

Retrospective test phase. One year of sepsis cases was selected based on ICD codes and was matched with a random one-year sample of non-sepsis cases admitted to the hospital from the ED for a total of 8,975 adult cases. Sepsis diagnosis was based on ICD-10 codes for sepsis or septic shock or the combination of an infection related ICD-10 code and a code for organ dysfunction. There were 1175 sepsis cases and 7800 non-sepsis cases based on the study definitions. The performance of the CDS varied widely between specific groups (see Table 6).

Group→	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
Sensitivity (%)	25.0	95.2	58.6	63.8	71.3	85.7	88.3	62.1	61.4	78.1	100	90.7	25.0	79.5%	71.4%
Specificity (%)	66.7	57.9	03.9	92.8	92.3	62.5	40.3	90.7	90.8	85.1	100	58.2	100	90.3%	89.6%
PPV (%)	33.3	45.6	51.5	45.7	46.8	66.7	46.9	50	42.2	44.1	66.7	52.7	100	50.0%	46.3%

Table 6: Distribution and performance of ISA on the larger test cohort of patients.

In this larger cohort, univariate analysis of current and potential variables were then assessed (Table 7). In multivariate logistic regression, MAP (OR 1.006; 95% CI 0.999,1.014), heart rate (OR 1.012; 95% CI 1.005, 1.020), respiratory rate (OR 1.037; 95% CI 1.024, 1.049), lactate (OR 1.134; 95% CI 1.074, 1.197), and creatinine (OR 1.100; 95% CI 1.028, 1.166) were associated with a sepsis diagnosis. Notable variables that were not statistically associated to a sepsis diagnosis included age, temperature, white blood cell count and anion gap.

	Non-Sepsis	Sepsis		
	Mean (SD)	Mean	Chi-square value	p
Age	55.19(17.98)	62.95(15.75)	-8.04	0.000
DBP (min)	72.12(18.37)	56.16(15.79)	16.19	0.000
SBP (min)	125.42(25.28)	96.32(26.29)	21.31	0.000
Mean Arterial Blood Pressure (Min)	91.11(18.04)	71.67(19.31)	19.82	0.000
Heart rate (max)	97.77(21.34)	116.58(24.95)	-16.22	0.000
Respiratory rate (max)	20.75(6.36)	27.1(11.02)	-17.81	0.000
Fraction of inspired oxygen (max)	66.7(30.23)	84.27(24.36)	-5.47	0.000
Temperature (max)	36.9(0.76)	37.52(1.44)	-14.52	0.000
Lactic Acid	2.4(2.5)	4.02(3.26)	-10.41	0.000
Sodium	138.65(4.81)	139.15(8.81)	-1.84	0.065
Creatinine	1.67(2.18)	2.58(2.09)	-7.71	0.000
BUN	21.6(19.36)	45.36(33.48)	-21.85	0.000
Anion gap	10.74(4.17)	13.98(5.7)	-14.02	0.000
HCO3	25.47(4.4)	23(6.1)	10.21	0.000
Platelet	261.44(108.9)	262.06(140.8)	-0.10	0.918
Glucose	144.13(105.22)	153.97(116.73)	-1.72	0.085
WBC	9.91(5.61)	14.69(8.12)	-15.43	0.000
Hemoglobin	144.13(105.22)	153.97(116.73)	-1.72	0.085
Potassium	4.09(0.76)	4.48(0.92)	-9.37	0.000
Troponin	0.33(2.08)	0.78(3.69)	-2.28	0.023
Ethanol	180.15(113.83)	44(22.517)	2.067	0.040
Chloride	102.45(5.16)	102.31(8.29)	0.46	0.646
BMI	39.97(808.28)	26.69(9.29)	0.24	0.811
Glasgow Coma Scale	14.42(2.04)	12.42(3.92)	14.77	0.000
History of sepsis	0.6	3.6	43.83	0.000

Table 7: Univariate analysis of current and potential ISA sepsis variables.

Implementation Phase Preparation for the implementation phase began well in advance of finalizing the model. These steps required a close working relationship with the information technology department of the Detroit Medical Center. The administrative leadership provided letters of support for our grant were fully aware and enthusiastic about this project. Despite early planning, competing priorities of the health system interfered with meeting with the chief medical officer and thus implementation was unavoidably delayed.

When the computer model was installed, there were multiple inconsistencies as compared to the model we had provided the programmers. Though the rule-based algorithm is transparent and straightforward, the programing can be complicated for a number of reasons. Some of the rules were implemented based on old thresholds which was due to a miscommunication on the part of the investigators; the old lactate rule gave three points; however we had adjusted it to 2 points for the final logic. This error, prior to correction, was accounting for 32% of all false positives.

Additional issues were related to ensuring that the exact coding and definitions were consistent from our model to the final programing. For instance, thresholds would change if a '=' was used in the formula instead of '>='. When the wrong formatting was used, the program would automatically rounded results to the nearest whole number. In the case of lactate levels and white blood cell counts, the rounding resulted marked changes. The lactate thresholds are all between 1.3-1.8; any rounding down to 1.0 or up to 2.0 would frequently change the result. A similar issue occurred with WBC. It required a few weeks of investigation on the part of the investigators and programmers. Once the specific error was discovered, the programmers were able to determine the issue by cross referencing our model with the code. There was a modest delay in being able to assess the final performance of the model due to these errors.

Live Validation Phase The final data for prospective analysis included all adult patients (>= 18 years at time of visit) seen in the emergency room of Sinai Grace hospital (Detroit, Michigan) between (inclusive) the dates of August 16th, 2018 and October 31st, 2018. This resulted in the ISD system monitoring a total of 18,412 unique patient encounters.

The gold standard used for sepsis in the phase was based on ICD-10 coding. The overall prevalence of sepsis in our sample was lower than expected at 0.92%. The model accurately discriminated patients into the separate 14 groups with 98% accuracy. The majority of group assignment discordance was due data missing from the EMR. For instance, if the patient was new to the system and the Problem List (from which the model populates the past medical history of end stage renal disease, multiple sclerosis or paraplegia) was not yet populated. Otherwise, the model functioned exactly as designed with respect to score determination and alert delivery to the investigator.

The final sensitivity, specificity and PPV of the model was 77.8%, 99.5% and 57.3%, respectively. This fell short of our target goal but and exceeds the performance of the active live sepsis clinical decision tool used in our hospital system (called the St. Johns Sepsis Alert). As noted in previous phases the group-specific performance varied widely reflectively both the heterogeneity of sepsis as well and the difficulty in creating an all-encompassing model.

DISCUSSION

The SSC cites the lack of routine, accurate sepsis identification as a major obstacle to providing evidence-based interventions that have been shown to improve patient outcomes.[25,26] The implementation of routine screening processes for sepsis are now strongly recommended for all patients.[26] The best, and arguably the only way to efficiently accomplish this is by utilizing a clinical decision support (CDS) tool, which is an alert software program interfacing with the electronic medical record (EMR). There are many reports of electronic or computerized surveillance systems to identify septic patients and to increase delivery of quality of care metrics.[21-23,27-51] Most EMR vendors have designed sepsis CDS tools. All of these systems rely on rudimentary logic and represent static scores based on common diagnostic criteria and apply them uniformly to all patients regardless of age, co-morbidities and other factors.

Some investigators have reported decreased time to delivery or improved quality of care measures related to the use of a sepsis CDS tool without reporting on the system's accuracy (sensitivity, specificity, negative and positive predictive values).[33,34] It is crucial, however, to report out an alert's accuracy to describe the proportion of "disease-positive" patients being missed and additionally false positive-alerts which contribute to unacceptable alert fatigue. In a recent systematic review, Makam et al identified eight reports (out of 1,293 in their initial search) that measured both performance of sepsis-related CDS tools and effect on outcomes.[21,22,34,41,42,45-48] Only five studies reported on the accuracy (sensitivity, specificity, positive predictive value) of CDS tools for identifying patients with sepsis.[21,41,45-47] Further, only three of these studies included ED patients (which are the focus of our proposal), one of which done by Meurer et al was limited to patients 70 years and older.[21,41,46] The two remaining studies involved 2,481 adult ED patients. Using rudimentary logic-driven criteria on a small ED sample (184 patients), Nelson et al reported sensitivity of 63.6%, specificity of 99.6% and a positive predictive value of 54% of their sepsis CDS program, which is currently the best reported performance in the literature. While Nguyen et al reported the positive predictive value of their logic-driven sepsis CDS tool in a large Level 1 trauma center was 44%, without reporting its sensitivity.

CDS tools with low positive predictive values generate a high percentage of false alerts and create a dangerous environment of alert fatigue. A Joint Commission study of ninety-eight alert events relating to alert fatigue reported that death resulted in eighty of the cases.[52] Providers become habituated to false alerts and begin to ignore even true positive alerts, thus creating a environment of harm.[53] False alarms can lead to desensitization of hospital staff that can lead to fatal consequenes.[52] It is vital for a CDS tool to optimize both of these characteristics simultaneously, which is also the goal of this proposed project.

There are no reports of CDS tools that treat patients differently in the screening of sepsis or that vary the screening logic based upon different patient categorizations, such as how ISA functions. This is in sharp contrast to how clinicians make diagnoses and contributes to the ongoing harmful errors of current sepsis CDSs tools. Because sepsis is an extraordinarily heterogeneous disease process that affects every age group and demographic, different patients may present with widely different clinical manifestations, making diagnostic rules in broad strokes inaccurate. A young, healthy patient with high heart rate and a fever may have a mild upper respiratory virus while a 76-year-old man with end stage renal disease on chronic dialysis with the same presentation may have severe sepsis and profound organ dysfunction.

Our ISA functioned well in a sample of 50% prevalence sepsis, however struggled to maintain a similar performance in a large sample and in prospective validation. The etiology behind much of variability is multifactorial and is related to host-specific issues, sepsis heterogeneity and EMR limitations. The model development in part suffered as the derivation straddled the transition from ICD-9 coding to ICD-10 coding. Additionally, the advent of the new ‘Sepsis 3.0’ guidelines occurred in the middle of the development and affects documentation and ultimately coding of these patients. Thought CMS does not yet utilized Sepsis 3.0, it is becoming the literature gold standard.

There are several novel topics that the development of ISA illustrates, however. There is no debate regarding the heterogeneity of sepsis and fact that precision medical is the ideal approach. Our data demonstrates a clear benefit following partitioning of patients into different risk groups. The sepsis diagnosis was far more confidence in some groups compared to others. This is a piece of data that could improve transparency and adoption among end users if the confidence of the alert was reported along with the result. In some patients, the sepsis alert my have high confidence (> 95%) while in another patient it may have only moderate confidence (70-80%).

To summarize, computerized CDS tools designed to identify sepsis in the ED have relatively low sensitivities and generate an unacceptable number of false positive alerts.[22,52] The difficulties in developing an accurate CDS tool for sepsis lies in the fact that sepsis is a very heterogeneous disease state in which patients may have a wide array of clinical manifestations. The Intelligent Sepsis-Alert developed in this study is built with a novel design and approach. The ultimate performance was moderate, however many valuable lessons were learned during its development which can be inform future initiatives.

LIMITATIONS

Despite early success in the derivation phase, the final performance fell short of *a priori* success. ISA improved on the specificity and PPV yet did not improved the sensitivity of the original SA model. A source of the discrepancy between the retrospective data and prospective data is multifactorial. This includes the prevalence of the sample which was near 50% in the retrospective cohort and 0.92% in the prospective set. Additionally, the retrospective data set has the advantage of being small enough to have had each and every case individually adjudicated for sepsis by the investigator. The model was derived essentially with a different gold standard (individually adjudicated cases) than it was validated on (ICD-10 codes). The investigators feel that this is justified considering the understood inaccuracies that ICD coding can have. Additionally, the ultimate goal to identify the “truth in the universe” which is the correct diagnosis at the bedside. This process, however, is not scalable, and the prospective performance analysis is completely dependent on the accuracy of the ICD-10 coding. As mentioned above, the model development suffers from the transition in ICD coding standards as well as the introduction of a new diagnostic standard for sepsis.

CONCLUSIONS AND FUTURE DIRECTIONS

Our ISA CDS demonstrated moderate success in the cohort of patients and results varied widely between subgroups of patients. Several valuable lessons were learned during the development of ISA. Partitioning of patients into separate risk groups appears to improve diagnostic yield of this CDS. The investigators are continuing to work with the hospital system and the IT to improve the performance of ISA. The team is utilizing the skills and knowledge gained to apply AI and machine learning techniques to related opportunities to improve sepsis management with regard to targeting patients for appropriate interventions and guiding fluid resuscitation and vasopressor administration.

The model also now has linkage to our (investigators') inpatient sepsis monitoring tool (called PreShock) which was specifically designed to identify admitted sepsis patients who at high risk for clinical deterioration. The PreShock tool was not part of the AHRQ protocol and was designed and implemented with a previous grant from Blue Cross Blue Shield of Michigan Foundation. All patients on whom ISA identifies as sepsis are electronically 'handed over' to the PreShock CDS which continues to monitor the patient based on a completely separate set of logic and identifies patients at high risk of clinical deterioration. The duel system functions independently as a diagnostic and then clinical monitoring tool. As of this writing, ISA has been continuously functioning in the DMC EMR. There have been 540 alerts delivered since November 1, 2018 through May 31st 2019.

LISTS OF PUBLICATIONS AND PRODUCTS

1. Sherwin, R, Ying H. et al. Performance of a Knowledge Based CDS and the Impact of Optimization and Patient Partitioning to identify ED patients with Sepsis. Annals of Emergency Medicine, Volume 70, Issue 4, Supplement, S13, October 2017
2. Thom S., Sherwin, R, Ying H. et al. Management Patterns and Outcomes of Patients with Severe Sepsis or Septic Shock Admitted from the Emergency Department with End Stage Renal Disease or Congestive Heart Failure. Annals of Emergency Medicine, Volume 70, Issue 4, Supplement, S151, October 2017
3. Sherwin, R, Ying H. et al. Results of 20 Machine-Learning Techniques to Identify Sepsis Patients in the Emergency Department Annals of Emergency Medicine, Volume 72 , Issue 4 , S6 - S7, October 2018
4. U.S. Provisional Patent Application No.: 62/543,038; Title: Intelligent Sepsis Alert; Reference No.: 10114-290

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